REMARKS

Upon entry of this amendment, claims 1, 4-6, 10, 16-18 and 20-32 will be pending and under consideration.

Claims 2 and 3 have been canceled in this response without prejudice. Claim 1 has been amended to incorporate the subject matter of claims 2 and 3. Claims 4 and 10 have been amended to correct the claim dependencies.

No new matter is added.

Rejection under 35 U.S.C. § 103(a)

Claims 1-6, 10, 16-18 and 20-32 are rejected under 35 U.S.C. § 103(a), as, allegedly, obvious over International Patent Publication No. WO 92/15285 by Lenz *et al.* ("Lenz"). According to the Examiner, given the teachings of Lenz, the claimed invention is obvious in view thereof.

Applicants respectfully disagree with the Examiner. Applicants note that claim 1 has been amended to recite that the method for producing a controlled release matrix comprises co-extruding through an extruder a composition comprising a dry mixture of at least one pharmaceutically active agent and at least one starch, wherein the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure, and wherein the co-extruding is under sheer force, temperature and pressure conditions such that the starch in the extruded controlled release matrix is vitrified. As is understood by those skilled in the art, the term "vitrified" indicates that the resulting matrix is hard and stiff and certainly not soft and rubbery. Furthermore, the term "vitrified" also implies that the starch matrices in accordance with the present invention are actually below the glass transition temperature. Further, Applicants note that the present specification clearly discloses that the essential controlled release properties of the matrix produced in accordance with the claimed methods, are determined by, and solely depend on, the specific extrusion parameters. Thus, according to the present invention, the release of the active agent from the matrix is directly dependent on the extrusion process parameters and is determined by these parameters. As a consequence, the resulting vitrified matrix, which comprises the active agent, can be used directly as an oral dosage form with controlled release behavior, without any further processing steps.

Lenz discloses compositions comprising (i) a matrix comprising starch having been processed under shear at temperatures of about 80°C to 240°C in a closed volume wherein the water content of the matrix was maintained at about 5% to about 45% by weight based on the starch/water mix, and (ii) an active ingredient. Preferably, the starch is processed to a specific

endothermic transition just prior to oxidation and thermal degradation. Note that the active ingredient is not processed with the starch but is merely combined with the starch after processing. See Lenz at page 11, lines 13-25; at page 14, lines 16-25. Moreover, the processed starch in Lenz, called molecularly dispersed starch or MDS, is not stiff or glassy, but, rather, is soft and rubbery, which allows the extruded MDS to be more compressible. See Lenz at page 28, lines 31-38, which teaches that the MDS obtained by extrusion is soft and rubbery. Even though both Lentz and the present invention teach destructurization of starch by way of extrusion, the nature of the destructured starch obtained is different since the molecularly dispersed starch of Lenz is soft and rubbery and, thus, above glass transition temperature. In fact, Lenz teaches at page X, lines y-z, that it is preferred that the process heats the starch above the glass transition temperature. The extruded matrices obtained by the present invention are vitrified, *i.e.*, rigid and, thus, their temperature never exceeded the glass transition temperature and preferably remains below the glass transition temperature. This structural differences between the starch matrices of the present invention and that of Lentz is a consequence of the differences in the disclosed methods, *inter alia*, wherein the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure.

The only passage in Lenz that concerns co-extrusion of a pharmaceutically active agent and a starch is on page 17, line 37 to page 18, line 1. However, there are absolutely no details in the Lenz specification on how such a co-extrusion can be carried out, unless the co-extrusion is carried out by the same methodology as Lenz uses to extruded the starch alone. Simply stating that co-extrusion is desirable cannot suggest the specific methods of the present invention. Applicants point out that Example 18 in Lenz, however, does provide details for a method of co-extrusion. However, Example 18 teaches co-extrusion of not starch but molecularly dispersed starch (which was previously extruded starch) with an active agent (clotrimazole) and talc. Further, as explicitly stated by Lenz, the resulting co-extruded product is a foamed product, which is not a controlled release matrix. The pending claims require that the matrix produced by the method be a vitrified controlled release matrix. A foamed product is not a vitrified product.

The Examiner has criticized Applicants for interpreting Lenz based solely on the Examples. Applicants submit that they have not done so. However, where the specification is silent on how to specifically carry out the co-extrusion, Applicants have no choice but to look to the sole Example where such a method of co-extrusion is disclosed for details on how to carry out the method in order to determine whether the method is the same or different from the claimed method and whether any differences are meaningful. Only once it is determined what the actual methodology entails, can one skilled in the art determine whether the disclosure of

Lenz fills in the gap between the teaching of Lenz and the claimed invention Applicants respectfully submit that the differences between the presently claimed methods and Lenz, *i.e.*, that the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure resulting in the production of a vitrified controlled release matrix, are not obvious in view of Lenz since Lenz does not suggest such specific methodology nor to modify the disclosed method to achieve the claimed methods. Further, with regard to the extruded product itself, Lenz does not teach or suggest such a vitrified product nor does Lenz teach or suggest how to modify the disclosed method to produce such a vitrified controlled release matrix.

Lentz teaches throughout the specification, including the Examples, the production of a starting material for a controlled release matrix. As taught on page 11, lines 26 to 29 of Lenz, the extrusion process only serves to destructure the starch to obtain the starting material, molecularly dispersed starch or MDS, which MDS is then processed further. Lentz clearly teaches that the MDS is only subsequently, *i.e.*, after the extrusion step, processed into a controlled release dosage form. Lenz does not suggest that the extruded starch, whether co-extruded with an active agent or not, can be used as a controlled release product prior to any other further processing. Page 15, lines 8-14 of Lenz discloses that controlled release is a consequence of the improved compressibility and/or density of the dosage form, thus, indicating that controlled release functionality is obtained upon compressing the MDS and active agent, *e.g.*, into a tablet. Thus, Lentz clearly discloses that the extrusion of the starch only serves to produce MDS as the starting material for further processing into a controlled release preparation. The controlled release matrix of Lenz is not directly obtained through extrusion even if the starch was co-extruded with the active agent. Such controlled release functionality is disclosed to be only a consequence of additional processing steps.

In contrast, the vitrified matrix produced by the presently claimed methods is below the glass transition temperature and is so rigid and stiff that it cannot be compressed into tablets, unlike MDS of Lenz. Nevertheless, these vitrified matricies provide controlled release functionality which can be used directly for controlled release preparations without the need of further processing.

A rejection for obviousness is improper when there is nothing in the cited prior art reference suggests the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill

would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). The suggestion of the claimed invention must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir 1988). In the present case, the presently claimed methods are directed to the production of a controlled release matrix by co-extrusion of a dry mixture of a starch and an active agent where the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure. Lenz does not teach or suggest a modification of its disclosed method requiring that the temperature at the orifice of the extruder during the extrusion process be below 100°C under normal pressure. Further, Lenz does not teach or suggest a vitrified controlled release matrix or one that is readily administerable without any additional processing steps.

Therefore, Applicants respectfully submit that Lentz does not render obvious the claimed subject matter and, therefore, respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks of the present response be entered and made of record in the file history present application. Applicants submit that the presently pending claims meet all requirements for patentability and respectfully request allowance and action for issuance.

Applicants request that the Examiner call the undersigned at (212) 326-3921 if any questions or issues remain.

Respectfully submitted,

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Enclosures